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REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

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Malformations of cerebral cortical development include a wide range of developmental disorders that are common causes of neurodevelopmental delay and epilepsy. In addition, study of these disorders contributes greatly to the understanding of normal brain development and its perturbations. The rapid recent evolution of molecular biology, genetics and imaging has resulted in an explosive increase in our knowledge of cerebral cortex development and in the number and types of malformations of cortical development that have been reported. These advances continue to modify our perception of these malformations. This review addresses recent changes in our perception of these disorders and proposes a modified classification based upon updates in our knowledge of cerebral cortical development.

Keywords: cerebral cortex; malformation of cortical development; microcephaly; cortical dysplasia; polymicrogyria

Abbreviations: FCD = focal cortical dysplasia

Introduction

Malformations of cortical development have been of interest to clinicians and neuroscientists for many decades (Friede, 1989; Sarnat, 1992; Norman *et al.*, 1995). In 1996, the term malformation of cortical development was introduced to designate a collectively common group of disorders in children with developmental delay and young people with epilepsy; a classification scheme was introduced, based upon the earliest developmental step at which the developmental process was disturbed

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(Barkovich *et al.*, 1996). Updates of the classification relied more heavily on genetics, and noted that the classification likely would never be finalized because of ongoing discoveries (Barkovich *et al.*, 2001, 2005). Since the last revision, many new syndromes have been described, and many new genes and mutations of known genes have been identified. A new classification has been proposed for focal cortical dysplasias (FCDs), and our knowledge of the molecular biology of both normal and abnormal cortical development has evolved.

This abundance of new information has largely fit well into the existing framework, but a few structural changes and the addition of new syndromes and genes were needed to remain consistent with current literature. Here we present an updated version of the classification. Many disorders listed in Appendix 1 and Supplementary Table 2 are not mentioned in the text because discussing all of them would make the article prohibitively long. The discussions, therefore, focus on those disorders that have conceptual importance whereas the tables attempt to include as many disorders as possible, recognizing that some will inevitably be missed. Hopefully, this update will prove useful for clinicians evaluating and treating affected patients, as well as for researchers investigating these important disorders.

Recent advances in embryology of cerebral cortical development

The cerebral cortex is a modular structure (Cholfin and Rubenstein, 2007; Cholfin and Rubenstein, 2008; Hoch *et al.*, 2009): modules of neurons are induced in a neuroepithelial sheet and subsequently differentiate, migrate and organize into a functioning cerebral cortex. Neuronal induction results from a combination of graded extracellular signals and transcription factor gradients that operate across several fields of neocortical progenitor cells (Sansom and Livesey, 2009). This process is regulated by interplay between intrinsic genetic mechanisms and extrinsic information relayed to cortex by thalamocortical input and other, largely unknown, factors (O'Leary *et al.*, 2007; Rakic *et al.*, 2009; Supplementary material).

Although details of the neural cell proliferation differ among mammalian species, GABAergic cortical interneurons are produced in the medial and caudal ganglionic eminences, and the subventricular zone of the pallial (dorsal) germinal epithelium (Petanjek *et al.*, 2009; Miyoshi *et al.*, 2010; Lui *et al.*, 2011) and migrate tangentially (from the medial ganglionic eminences) or radially (from the dorsal subventricular zone) to the developing cortex. The precise details in humans are not yet known (Lui *et al.*, 2011). In the dorsal subventricular zone, neuroepithelial cells differentiate into radial glial cells, in part promoted by fibroblast growth factor (Sahara and O'Leary, 2009). Whereas neuroepithelial cells divide symmetrically to expand their numbers, radial glial cells divide asymmetrically to both self-renew and generate restricted intermediate progenitor cells, which divide symmetrically to produce two or more neurons but no progenitors. Both radial glial and intermediate progenitor cells produce glutamatergic neurons (Merkle and Alvarez-Buylla, 2006; Kang *et al.*, 2009). Another class of precursor cells in the dorsal ventricular zone, the short neural precursors, appear to be committed to symmetrical neurogenic divisions (Howard *et al.*, 2006; Stancik *et al.*, 2010).

Based upon interspecies comparisons, the generation of increased numbers of intermediate progenitor cells underlies increased cortical complexity and size (Kriegstein *et al.*, 2006). Thus, the balance between self-renewal and progression to a more restricted state is a critical factor in regulating the number of intermediate progenitor cells, and ultimately, cortical size. The mechanisms that regulate this progression are poorly understood (Elias *et al.*, 2008; Mérot *et al.*, 2009; Subramanian and Tole, 2009; Lui *et al.*, 2011). However, mutations have been found in genes regulating the progenitor cell mitotic cycle in several types of severe congenital microcephaly (Thornton and Woods, 2009; Yu *et al.*, 2010; Castiel *et al.*, 2011; Kalay *et al.*, 2011). Further, human microcephaly syndromes can be classified, to some degree, by the affected cell cycle phase (Supplementary Table 1).

Understanding of cell proliferation has been aided by the discovery that the primate subventricular zone is complex, composed of an outer subventricular zone, a layer of radially oriented neurons that is divided from the underlying subventricular zone by an 'inner fibre layer' that is presumably composed of corticocortical, corticothalamic and thalamocortical axons (Smart *et al.*, 2002; Zecevic *et al.*, 2005). Large numbers of radial glial-like cells and intermediate progenitor cells populate the human outer subventricular zone. The radial glial-like cells are non-epithelial, as they lack contact with the neuroependyma of the ventricular surface (Hansen *et al.*, 2010), but still undergo both symmetric and self-renewing asymmetric divisions that allow further proliferation (Hansen *et al.*, 2010). The expansive proliferation of progenitor cells in the outer subventricular zone helps to explain the evolutionary expansion of the number of radial glial units, surface area and gyrification in the primate cortex, as these later-born cells are presumed to occupy the outer cortical layers (Zecevic *et al.*, 2005; Lui *et al.*, 2011).

Recent advances in the genetics of cortical development

Progress has been made in understanding neuronal migration at the intracellular level (Heng *et al.*, 2008; Nóbrega-Pereira *et al.*, 2008; Stanco *et al.*, 2009; Marin *et al.*, 2010). As the importance of microtubule transport, centrosomal positioning, nuclear transport (associated with LIS1), microtubule stabilization (associated with DCX), vesicle trafficking and fusion (ARFGEF2 and FLNA), and neuroependymal integrity (MEKK4 and FLNA) in neuronal migration are well known (Wynshaw-Boris, 2007; Ferland *et al.*, 2009; Pramparo *et al.*, 2010), it was not surprising that mutations affecting microtubule proteins TUBA1A, TUBA8, TUBB2B and TUBB3 are associated with abnormal neuronal migration (lissencephaly) and postmigrational development (polymicrogyria or polymicrogyria-like dysplasias) (Poirier *et al.*, 2007; Abdollahi

et al., 2009; Jaglin and Chelly, 2009; Kumar *et al.*, 2010; Poirier *et al.*, 2010). Many genes linked to several pathways are known to regulate neuronal migration, but the mechanisms are poorly understood. Knockdown of some genes (such as *Rnd2*) result in migration defects that are identical to those observed with deletions of others (such as Neurog2) (Heng *et al.*, 2008). Proteins that function in anchoring of the radial glial cells to the ventricular epithelium (such as BIG2; Ferland *et al.*, 2009) or to the pial limiting membrane (such as GPR56; Luo *et al.*, 2011) affect migration in a manner similar to those that directly affect migration. Clearly, any classification based upon these genes will require changes as the mechanisms of action of their protein products are elucidated.

The processes that direct postmitotic neurons in the ventricular and subventricular zones are being elucidated. In mice, neurons in the medial ganglionic eminences migrate to the striatum because *Nkx2-1* (human *NKX2.1* or *TITF1*) regulates expression of neuropilin-2, a guidance receptor that enables interneurons to enter the developing striatum. When *Nkx2-1* is downregulated, interneurons are repulsed by class 3 semaphorins and bypass the striatum, migrating instead to the cortex (Nóbrega-Pereira *et al.*, 2008; Hernández-Miranda *et al.*, 2011). The laminar fate of neurons is determined in progenitor cells prior to their final mitosis. Early cortical progenitors are competent to generate late-born neurons after transplantation into older hosts, indicating that they can respond to later environmental cues, but progenitors become progressively restricted in their ability to populate different lamina as neurogenesis proceeds (Lui *et al.*, 2011). Neuronal genes that correlate with their layer-specific neuronal identity are selectively expressed by cortical progenitors. Many continue to be expressed in their progeny (Chen *et al.*, 2008; Lai *et al.*, 2008), and some exhibit very high laminar specificity in the cortex in both animals and humans. Examples include *Ror-beta* (in 50% of layer IV neurons), *Er81* (in 31% of layer V neurons) and *Nurr1* in layer VI (Hevner, 2007; Garbelli *et al.*, 2009).

Newborn projection neurons pause in the subventricular zone for up to 24 h before initiating radial migration, suggesting that the subventricular zone constitutes a unique 'permissive' environment for synchronizing migration by projection neurons and interneurons generated at the same time, thereby giving them their appropriate laminar identity (Mérot *et al.*, 2009; Lui *et al.*, 2011). In contrast, late cortical progenitors generate only upper layer neurons, even when transplanted into the more permissive environment of younger embryos (Lui *et al.*, 2011). Thus, the expression of many early neural genes appears to be 'turned off' as neurogenesis proceeds. These factors may provide clues to genes and pathways underlying malformations of abnormal postmigrational development (formerly malformations of cortical organization) such as polymicrogyria. Misspecification of projection, commissural and association neurons could potentially underlie disorders of sensorimotor or visual function, commissuration or cognition, respectively.

The developing leptomeninges affect multiple stages of cortical development. For example, retinoic acid produced in the leptomeninges regulates the generation of cortical neurons (Siegenthaler *et al.*, 2009). Tangential migration of cortical hem-derived Cajal–Retzius cells, which play an important role in termination of neuronal migration to the cortex, is controlled by the leptomeninges via CXCL12/CXCR4 signalling (Borrell and Marin, 2006). The leptomeninges are also essential for the survival of radial glial cells, which undergo apoptotic cell death if the meninges are removed (Radokovits *et al.*, 2009). Finally, the leptomeninges play an important role in maintaining the cerebral basement membrane. Loss of *Zic* activity reduces proliferation of meningeal cells, resulting in a thin and disrupted pial basement membrane in mouse models (Inoue *et al.*, 2008). Reduction of *Foxc1* activity in the leptomeninges impairs the ability of the basement membrane to expand in conjunction with brain growth, resulting in lamination defects, neuronal overmigration and subpial heterotopia formation (Hecht *et al.*, 2010). Thus, abnormal leptomeningeal development may result in cortical dysgenesis via multiple mechanisms.

Discussion and rationale for changes in new classification

Mutations of many genes have been newly described in patients with malformations of cortical development and these, along with the new advances concerning normal development discussed in the previous section, form the basis for this update. The overall framework of the classification remains largely the same (Appendix 1 and Supplementary Table 2) making it useful in everyday practice, while providing a theoretical basis for posing of academic questions. Group I remains 'Malformations secondary to abnormal neuronal and glial proliferation or apoptosis' and Group II remains 'Malformations Secondary to Abnormal Neuronal Migration'. The name of Group III has been changed from 'Malformations secondary to abnormal cortical organization' to 'Malformations secondary to Abnormal Postmigrational Development', as the process of cortical organization begins before the termination of neuronal migration. Another structural change is that Group IV, 'Malformations of cortical development, Not otherwise classified', has been eliminated and the disorders previously listed there have been moved. A third change is that disorders are classified according to their mode of inheritance (autosomal recessive, autosomal dominant, X-linked, polygenic in rare cases, etc.) and whether the disorder is clinically or genetically defined. This change should help clinicians classify their patients more easily, particularly in complicated disorders such as microcephalies. One concern is that the division into genetically defined and clinically defined disorders moves the classification, at least partially, from one based upon underlying mechanisms to one based upon current understanding. With the proliferation of gene discovery, it has become clear that different mutations of the same gene can result in completely different syndromes; thus, disorders defined by gene alone quickly become excessive and confusing. The optimal classification will not be based on genes but pathways and mechanism of protein action, with variations based on how the specific gene mutation alters protein function in the affected pathway. Clinically defined disorders may rapidly become obsolete. However, our current

understanding of pathways and mechanisms of protein action is not adequate to classify disorders on that basis, while genetic knowledge has advanced to the point where the old classification was becoming less useful. This revision can be viewed as an intermediate system that should prove useful while the foundations of the pathway-based classification are constructed. Genes, genetic loci and references for each disorder are in Appendix 1. The references should make Appendix 1 more useful to clinicians trying to make a diagnosis. Some disorders in Appendix 1 have no associated reference, either because they are well known and can be accessed in any textbook (such as ganglioglioma or isolated periventricular nodular heterotopia), or because the specific entities are not published, but have been identified as specific entities by the authors.

Group I: malformations secondary to abnormal neuronal and glial proliferation or apoptosis

This group continues to be separated into three categories: reduced proliferation or accelerated apoptosis (congenital microcephalies); increased proliferation or decreased apoptosis (megalencephalies); and abnormal proliferation (focal and diffuse dysgenesis and dysplasia).

Groups I.A and III.D: microcephaly

Most genes known to cause primary microcephaly (Appendix 1) affect pathways involving neurogenesis: transcription regulation (*MCPH1*, *CENPJ*, *CDK5RAP2*; Thornton and Woods, 2009), cell cycle progression and checkpoint regulation (*MCPH1*, *CENPJ*, *CDK5RAP2*; Thornton and Woods, 2009), centrosome maturation (*CDK5RAP2* and *CENPJ*; Thornton and Woods, 2009), dynein binding and centrosome duplication (*NDE1*; Alkuraya *et al.*, 2011; Bakircioglu *et al.*, 2011), DNA repair (*MCPH1*; Thornton and Woods, 2009), progenitor proliferative capacity (*ASPM* and *STIL*; Desir *et al.*, 2008; Kumar *et al.*, 2009; Passemard *et al.*, 2009), interference with mitotic spindle formation [*WDR62* (Bilgüvar *et al.*, 2010; Yu *et al.*, 2010) and *NDE1* (Feng and Walsh, 2004)] and DNA repair deficit [*PNKP* (Shen *et al.*, 2010) and *PCNT* (Griffith *et al.*, 2008)]. These pathways affect processes—alterations of cell cycle length, spindle positioning or DNA repair efficiency—that affect neurogenesis and, in particular, the cell cycle phases of mitosis (Supplementary Table 1). WDR62, ASPM and STIL are spindle pole proteins, suggesting that focused spindle poles are of great significance in neural progenitor cell division. Spindle poles attach to mature centrosomes; they control the position of the central spindle and, hence, the direction of the last stage of the cytokinesis cleavage furrow (Nicholas *et al.*, 2010). If cell division is perfectly symmetric, it produces two daughter cell neural precursors. If not, the daughter cell may fail to inherit a part of the cadherin hole; as a result, it differentiates into a neuron, becomes postmitotic, and migrates out of the neuroepithelium (Nicholas *et al.*, 2010). Microcephaly secondary to mutations of *WDR62* has associated cortical malformations (Yu *et al.*, 2010). Mutations of *ARFGEF2* have associated periventricular nodular heterotopia (de Wit *et al.*, 2009) and some individuals with microcephalic osteodysplastic primordial dwarfism have cortical dysgenesis (Juric-Sekhar *et al.*, 2011). Mutations of other primary microcephaly genes described so far do not have obvious brain anomalies other than simplification of the gyral pattern and hypoplasia of the corpus callosum (Passemard *et al.*, 2009; Rimol *et al.*, 2010; Shen *et al.*, 2010), although few have had pathological analyses. No definable clinico-radiological characteristics have been identified that separate microcephalies caused by mutations affecting different parts of the mitotic cycle. Although no human microcephaly syndromes have yet been described in association with excessive developmental neuron apoptosis, AMSH-deficient mice have been shown to have postmigrational microcephaly due to increased developmental neuronal death (Ishii *et al.*, 2001). Overall, a great deal of progress has been made in the understanding of genetic causes of microcephaly but not enough to justify a purely genetic- or pathway-based classification. Therefore, for the current classification, microcephalies are classified based upon inheritance, associated clinical features, and causative gene.

Patients born with normal to slightly small head size (2 standard deviations or less below mean) and developing severe microcephaly in the first 1–2 years after birth form a separate group designated postmigrational microcephaly (now listed in Group III), because brain growth seems to slow during late gestation or the early postnatal period after normal early development. X-linked postmigrational microcephaly associated with mutations of *CASK* is placed in this group; this disorder is seen in girls with mental retardation, short stature, and disproportionate cerebellar and brainstem hypoplasia (Najm *et al.*, 2008; Takanashi *et al.*, 2010). Also in this group are pontocerebellar hypoplasias due to mutations in transfer RNA splicing endonuclease subunit genes (*TSEN54*, *TSEN2*, *TSEN34*), prenatal onset neurodegenerative disorders in which significant microcephaly develops after birth (Barth *et al.*, 2007; Namavar *et al.*, 2011). Also in this group is microcephaly due to mutations or genomic deletions of *FOXG1*, sometimes described as a congenital variant of Rett syndrome (Kortüm *et al.*, 2011). The processes that interfere with normal brain development in late gestation or the early postnatal period are not understood. With the disruption of normal brain development occurring late, these disorders may be good candidates for intervention once the molecular cause of the disorder is understood.

Group I.B: megalencephalies

As reasons for megalencephaly are not established in many disorders in this group, many are clinically defined, even if the mutated gene is known. Megalencephaly is seen in 6% of patients with polymicrogyria (Leventer *et al.*, 2010). These megalencephalic polymicrogyria syndromes have been named macrocephaly, polymicrogyria, polydactyly, hydrocephalus (MPPH) (Mirzaa *et al.*, 2004), Macrocephaly–Cutis Marmorata Telangiectata Congenita (M-CMTC) and the Macrocephaly Capillary

Malformation (MCAP) syndromes (Conway *et al.*, 2007; Tore *et al.*, 2009). Nearly all of these patients have some sort of cortical malformation; most have perisylvian polymicrogyria, but the polymicrogyria may be more widely scattered and is sometimes more severe over the convexities. Progressive tonsillar ectopia (herniation) is characteristic. Until the different entities are sorted out, we have chosen to list all patients with polymicrogyria and macrocephaly within a single group, called MCAP (megalencephaly capillary malformation-polymicrogyria). Further subcategories will likely be established based upon genetic findings and associated anomalies.

Hemimegalencephaly is not included in this group because of the presence of abnormal (dysmorphic) cells in that disorder (Flores-Sarnat *et al.*, 2003).

Group I.C: cortical dysgeneses with abnormal cell proliferation

An important advance in understanding cell proliferation has been the elucidation of specific molecular pathways that control proliferation, in particular the mammalian target of rapamycin (mTOR) pathway, which is important in abnormal cerebral cortical development (as well as renal, cardiac and pulmonary development) of the tuberous sclerosis complex (Crino *et al.*, 2006). The tuberous sclerosis complex1–tuberous sclerosis complex2 protein complex integrates cues from growth factors, the cell cycle and nutrients to regulate the activity of mTOR, p70S6 kinase (S6K), 4E-BP1 and ribosomal S6 proteins. A number of groups have contributed to work showing that mutations leading to loss of function of the *tuberous sclerosis complex1* or *tuberous sclerosis complex2* genes result in enhanced Rheb-GTP signalling and consequent mTOR activation, causing increased cell growth, ribosome biogenesis and messenger RNA translation; ultimately, the result is overgrowth of normal cells and production of abnormal cells in many organs (Crino *et al.*, 2006). This discovery has had significant therapeutic implications in managing cerebral, visceral and cognitive disorders associated with tuberous sclerosis (de Vries, 2010).

A major change in this group has been the proposal of a new classification of FCDs, a heterogeneous group of disorders that commonly cause medically refractory epilepsy in children (Taylor *et al.*, 1971; Blümcke *et al.*, 2011). FCDs are very likely to have many aetiologies (Krsek *et al.*, 2010; Orlova *et al.*, 2010; Blümcke *et al.*, 2011). The new classification and several other works support the classification of FCD type II (FCDII) as a malformation due to abnormal proliferation. Histological characteristics of FCDII are fairly consistent across affected patients and it is likely to be a much more homogeneous disorder than FCDI or the new FCDIII (both discussed in the 'Group III: Malformations secondary to abnormal postmigrational development' section). Several groups have demonstrated that FCDI and FCDII cells (neurons and balloon cells) express different proteins at different cortical layers (Hadjivassiliou *et al.*, 2010; Orlova *et al.*, 2010). The protein phenotype of cells found in FCDII is similar to that seen in tubers of the tuberous sclerosis complex, justifying their classification together; both have progenitor proteins that appear early in development, are present in deep cell layers, and are similar to those found in multipotent or pluripotent stem cells. In contrast, cells from FCDI express few early proteins (Hadjivassiliou *et al.*, 2010; Orlova *et al.*, 2010) and those expressed are found in more superficial layers (junction of layers I and II) (Hadjivassiliou *et al.*, 2010). Other studies (Yasin *et al.*, 2010; Han *et al.*, 2011) suggest that balloon cells in patients with FCDII originate from glioneuronal progenitor cells, strongly suggesting that defects of neuronal and glial specifications are important in the histogenesis of FCDII. These findings support the concept that cells of FCDII derive from radial glial progenitors (Lamparello *et al.*, 2007) and may support the 'dysmature cerebral developmental hypothesis' that seizures in some forms of FCD may be the result of interactions of dysmature cells with normal postnatal ones (Cepeda *et al.*, 2006). Focal transmantle dysplasia (Barkovich *et al.*, 1997) and bottom of sulcus dysplasia (Hofman *et al.*, 2011), described as specific types of cortical dysplasia based on imaging features, have histological features of FCDIIb and are likely different names for the same entity (Krsek *et al.*, 2010). They have excellent outcomes after surgical resection, probably because their presence and location are easily identified by imaging (Krsek *et al.*, 2010).

Several authors have made the observation that hemimegalencephaly has increased cell densities in the outer cortical layers and white matter of the affected hemisphere, but decreased cell densities in the inner cortical layers (Salamon *et al.*, 2006; Mathern *et al.*, 2007). MRI studies showed that the non-affected hemisphere was smaller than hemispheres of age-matched normal subjects, resulting in the suggestion that somatic mutations affect each developing cerebral hemisphere differently (Salamon *et al.*, 2006), possibly due to incomplete apoptosis (Mathern *et al.*, 2007). The abnormal contralateral hemisphere may explain the poorer than expected post-surgery seizure control and cognitive outcomes (Salamon *et al.*, 2006; Mathern *et al.*, 2007). Hemimegalencephaly is divided into three categories because the appearance of hemimegalencephaly associated with tuberous sclerosis is one of multiple tubers in a single hemisphere (Griffiths *et al.*, 1998; Galluzzi *et al.*, 2002; Parmar *et al.*, 2003), rather than the more diffuse process involving a variable portion of a hemisphere, seen in other neurocutaneous disorders and in isolated hemimegalencephaly. This classification will need to be re-evaluated as more cases are carefully analysed.

Group II: malformations due to abnormal neuronal migration

Several studies have shown that abnormalities of the neuroependyma (ventricular epithelium) are associated with periventricular nodular heterotopia (Ferland *et al.*, 2009). Group II has, therefore, been divided into four subcategories: malformations resulting from abnormalities of the neuroependymal (initiation of migration), mainly including periventricular heterotopia; generalized abnormalities of transmantle migration, mainly including lissencephalies; localized abnormalities of transmantle migration, mainly subcortical heterotopia; and abnormalities due to abnormal terminal

migration/defects in pial limiting membrane. The latter group now consists mostly of cobblestone malformations, although less severe forms of these have been defined in foetal alcohol syndrome and in mice with mutations of some transcription factors such as Foxc1 (Zarbalis *et al.*, 2007).

Group II.A: heterotopia

Macroscopic collections of heterotopic neurons come in many forms and sizes, ranging from periventricular nodular heterotopia, the most common form, to periventricular linear heterotopia, consisting of a smooth layer of grey matter lining the ventricular wall, to columnar heterotopia, a linearly arranged collection of neurons that span the cerebral mantle from the pia to the ependyma, to large subcortical heterotopia that consist of curvilinear swirls of grey matter originating from deep sulci, which wind their way through the cerebral mantle to the ependyma. Little is known about the genetic and embryological causes of the more complex heterotopia. As the neurons are deposited everywhere between the ventricle and the pia in these disorders, they remain classified as malformations due to abnormal neuron migration. However, as periventricular nodular heterotopia appears to have a different embryogenesis than other heterotopia, and many have known genetic causes, they have been separated from the others and placed in the subcategory of malformations with neuroependymal abnormalities (Group II.A).

Ferland *et al*. (2009) showed that injury to, or denudation of, the neuroependyma (ventricular zone epithelium) is likely an important factor in the formation of periventricular nodular heterotopia (rather than a cell-intrinsic motility defect. This observation clarifies why periventricular nodular heterotopia is caused by *ARFGEF1* mutations even though its protein product (BIG2) is not involved in neuronal migration (Ferland *et al.*, 2009). Similar to subpial heterotopia in cobblestone malformations, which result from a loss of structural integrity of the pial limiting membrane (Yamamoto *et al.*, 2004; Luo *et al.*, 2011), the denuded ventricular epithelium in periventricular nodular heterotopia may cause disengagement of radial glia, resulting in an inability of young neurons to migrate away (Ferland *et al.*, 2009). Neurons in periventricular nodular heterotopia seem to be arranged in a layered pattern (Garbelli *et al.*, 2009); analysis of layer-specific genes suggests that the outer layer of neurons in the nodule is composed of layer 6 neurons (expressing *Rorβ*), with the next layer being composed of layer 5 (expressing *Er81*) and the next for layer 4 (expressing *Nurr1*) (Garbelli *et al.*, 2009). Compared with controls, fewer cells in the overlying cortex expressed these three genes in the appropriate layers, suggesting that late migrating neurons are less affected (Garbelli *et al.*, 2009).

Group II.B: lissencephaly

Malformations due to widespread abnormal transmantle migration including agyria, pachygyria and subcortical band heterotopia, are all part of the lissencephaly spectrum. A major change in this group has come from the discovery that mutations of *TUBA1A* are responsible for 1–4% of classic (four-layered, with a cell-sparse zone) lissencephalies (Morris-Rosendahl *et al.*, 2008; Kumar *et al.*, 2010) and 30% of lissencephalies with cerebellar hypoplasia (Kumar *et al.*, 2010). The *TUBA1A*-associated classic lissencephalies can have a wide range of dysgenesis involving the cortex, corpus callosum, basal ganglia/white matter and mid/hindbrain (Kumar *et al.*, 2010). Patients with *TUBA1A*-associated classic lissencephaly have either p.R402C mutations, resulting in frontal pachygyria and posterior agyria with a cell-sparse zone, or p.R402H mutations, resulting in nearly complete agyria; both of these phenotypes are essentially identical to those associated with *LIS1* mutations (Kumar *et al.*, 2010), suggesting involvement of the same molecular pathways. Other groups with *TUBA1A*-associated lissencephaly had variant lissencephaly with heterogeneous missense mutations throughout the gene resulting in cortical dysgenesis varying from diffuse, often asymmetric, pachygyria with moderately thick cortex to a smooth, relatively thin cortex associated with diminution of cerebral white matter (Kumar *et al.*, 2010). These phenotypes had absent or nearly absent corpus callosum, thin brainstem and severe cerebellar hypoplasia; callosal and mid-hindbrain malformations were most severe in the patients with thinner cerebral cortex (Kumar *et al.*, 2010). Some patients have upward rotation of the cerebellar vermis with a dilated fourth ventricle and enlarged posterior fossa, fulfilling the criteria for Dandy–Walker malformation (Kumar *et al.*, 2010). In our prior classification, these phenotypes were listed as variant lissencephaly with extreme microcephaly, absent (or nearly absent) corpus callosum, moderate to severe cerebellar hypoplasia and brainstem hypoplasia; they are likely the malformation that Forman *et al*. (2005) called 'two layer lissencephaly'. The clinical phenotypes caused by mutations of *TUBA1A* also vary considerably; however, most affected patients have congenital microcephaly, mental retardation and severe neurodevelopmental delay with di/tetraplegia (Bahi-Buisson *et al.*, 2008).

Group II.C: subcortical heterotopia and sublobar dysplasia

Subcortical heterotopia are poorly understood malformations in which large collections of neurons are found regionally in the deep cerebral white matter (Barkovich, 2000). Some are transmantle, composed of linear (columnar heterotopia) or curvilinear, swirling nodules of neurons continuous from the ependyma to the cortex. Others are composed of multiple nodules of neurons localized to the deep cerebral white matter. In all, the involved portion of the affected hemisphere is abnormally small and the overlying cortex appears thin, and sometimes, microgyric. The histology and embryogenesis of these disorders is unknown, but they are presumably due to localized abnormal late migration.

Also included in this category is sublobar dysplasia, a very rare malformation characterized by a region of dysmorphic brain within an otherwise normal-appearing hemisphere (Barkovich and Peacock, 1998). Histopathology, recently reported in a single patient, showed leptomeningeal and subcortical heterotopia, disturbance of cortical lamination, and marked cortical and subcortical astrocytosis, but no dysmorphic cells (Tuxhorn *et al.*, 2009).

As the early of these features correspond to abnormal cell migration, this disorder was moved to Group II.C.

Group II.D: cobblestone malformations

It has become clear that mutations of any genes involved in O-glycosylation of α-dystroglycan can cause a wide range of disorders ranging from Walker–Warburg syndrome to muscle–eye–brain disease to Fukuyama congenital muscular dystrophy to congenital muscular dystrophy types 1C and 1D to limb-girdle (LGMD2I, LGMD2K, LGMD2M) muscular dystrophies (Barresi and Campbell, 2006; Godfrey *et al.*, 2007; Clement *et al.*, 2008; Hewitt, 2009; van Reeuwijk *et al.*, 2010). The precise molecular mechanisms underlying these phenotypic variations are slowly being elucidated (Hewitt, 2009; Ackroyd *et al.*, 2011; Luo *et al.*, 2011). The cause of the muscular, ocular or brain disorders in these patients is defective formation of basement membranes (of skeletal muscle, retina and cerebrum/cerebellum, respectively), which is related to impaired linkage of radial glia to the pial basement membrane, which is, in turn, dependent upon O-mannosylation of α-dystroglycan (Barresi and Campbell, 2006; Hewitt, 2009), laminin α1 deposition (Ackroyd *et al.*, 2011) and GPR56-collagen III interactions (Luo *et al.*, 2011). Resulting deficiencies in the cerebral basement membranes result in impaired anchorage of radial glial cells to the basement membranes, causing abnormal cortical lamination and overmigration of neurons through the incomplete basement membrane into the pial layer (Li *et al.*, 2008; Luo *et al.*, 2011). Less severe mutations may partially allow development of basement membranes and result in a less severe phenotype (Barresi and Campbell, 2006; van Reeuwijk *et al.*, 2010; Luo *et al.*, 2011; Yis *et al.*, 2011). No direct correlation has been found between the severity of clinical disease and the particular gene mutation; however, null mutations of nearly all causative glycosylation genes result in severe (Walker–Warburg syndrome) phenotypes (except for *POMGnT1*) (van Reeuwijk *et al.*, 2010). Much recent work has focused on cobblestone malformations due to *Gpr56* and *Col4a1* mutations (Li *et al.*, 2008; Luo *et al.*, 2011) and malformations associated with several genes affecting glycosylation within the endoplasmic reticulum or Golgi apparatus (classified as congenital disorders of glycosylation). Concerning the latter, the two best documented disorders to date are *SRD5A3* (Al-Gazali *et al.*, 2008; Cantagrel *et al.*, 2010) and *ATP6V0A2* (Kornak *et al.*, 2008; Van Maldergem *et al.*, 2008). *GPR56* mutations appear to cause a 'cobblestone cortex' and not true polymicrogyria (Piao *et al.*, 2005; Bahi-Buisson *et al.*, 2010); therefore, the term 'frontoparietal polymicrogyria', which was the original name given to the cortical malformations seen in patients with *GPR56* mutations, would be better replaced with a more appropriate one, such as 'frontal-predominant cobblestone malformation'. The cortical malformation associated with *TUBB2B* mutations also has cobblestone-like features including overmigration of neurons through gaps in the leptomeninges (Jaglin *et al.*, 2009). Its proper classification awaits further study, but it is currently classified in Group III.A.3, syndromes with polymicrogyria, the neuropathology of which may differ from classic polymicrogyria.

Group III: malformations secondary to abnormal postmigrational development

Group III.A: polymicrogyria and schizencephaly

Polymicrogyria has been known for many years to be a spectrum of disorders classified under a single name and many discussions of 'true' polymicrogyria and variants of microgyria have appeared in the literature (Volpe and Adams, 1972; Evrard *et al.*, 1989; Barkovich, 2010*a*). However, the term is still widely used to describe disorders that have different causes, somewhat different gross appearance, association with different accompanying malformations or disruptions, and different microscopic appearance, making it difficult to understand and properly classify the disorders (Judkins *et al.*, 2011). Polymicrogyria has been described in conjunction with many genetic disorders (listed in Appendix 1, Group III.A.3). Unfortunately, little is understood of the range of histopathology seen in polymicrogyria, partly because few large scale pathological studies have been performed. The paucity of pathological data stems from polymicrogyria often being located in eloquent cortical areas; thus, it is rarely resected when causing intractable epilepsy (Leventer *et al.*, 2010). Recent studies suggest a great deal of heterogeneity in the gross (Barkovich, 2010*b*; Leventer *et al.*, 2010) and microscopic (Judkins *et al.*, 2011) appearance of polymicrogyria, supporting the concept that polymicrogyria is heterogeneous in cause, embryogenesis and gross characteristics. In addition, it has been speculated that the underlying mechanisms by which polymicrogyria develops in patients with mutations and infections may be vascular (Robin *et al.*, 2006). Many authors describe malformations resulting from disruption of the radial glial fibre attachment to the pial limiting membrane and the consequent gaps in that membrane as polymicrogyria (Jaglin and Chelly, 2009), but (as discussed in the previous section) others believe that cortical malformations associated with pial membrane defects are distinct from polymicrogyria and are better classified as cobblestone malformations (Jansen and Andermann, 2005; Leventer *et al.*, 2010; Judkins *et al.*, 2011). To determine the mechanisms leading to polymicrogyria, a first step will be to perform histological and molecular studies on resected tissue or autopsy specimens, in addition to developing appropriate animal models, before the differences among the many patterns can be understood.

In this classification, we have put polymicrogyria into four groups: Group III.A. with schizencephalic clefts or calcifications, presumably due to infection or vascular causes; Group III.B. without clefts or calcifications, which may be genetic or disruptive; Group III.C. as part of genetically defined multiple congenital anomaly syndromes (some of these have atypical histology); and Group III.D. in conjunction with inborn errors of metabolism (these also have atypical histology). These groups should be refined as new studies of the pathology and pathogenesis of polymicrogyria are performed.

Although past work suggested that mutations of *EMX2* are a common cause of schizencephaly (Granata *et al.*, 1997), recent work has shown that *EMX2* mutations are highly unlikely to be a cause of schizencephaly (Tietjen *et al.*, 2007; Merello *et al.*, 2008); the authors recommend against testing for this gene, as the results would be uninterpretable. Furthermore, a large population study of <4 million births in California from 1984 to 2001 found an association with young maternal age and with monozygotic twin pregnancies (Curry *et al.*, 2005). One-third of cases had a non-CNS abnormality, over half of which could be classified as secondary to vascular disruption (including gastroschisis, bowel atresias and amniotic band syndrome) (Curry *et al.*, 2005). The authors concluded that schizencephaly is a disorder with heterogeneous causes, many of which are vascular disruptive in origin (Curry *et al.*, 2005). It is unquestionably associated with polymicrogyria of disruptive aetiology. Accordingly, it is classified in Group III.A and by clinical characteristics.

Group III.C: focal cortical dysplasias

Certain FCDs are classified as 'Malformations secondary to abnormal postmigrational development' because evidence supports proposals that they can result from injury to the cortex during later stages of cortical development. Evidence has been published that prenatal and perinatal insults including severe prematurity, asphyxia, shaking injury, bleeding, hydrocephalus and stroke, occur in children with mild malformation of cortical development or FCDI (Marin-Padilla *et al.*, 2002; Krsek *et al.*, 2010). Patients with significant prenatal and perinatal risk factors had more abnormal neurological findings, lower IQ scores, and slower background EEG activity than subjects with mild malformation of cortical development/FCD without prenatal or perinatal brain injury (Krsek *et al.*, 2010). As FCDIII are, by definition, associated with injury, vascular malformation or epileptogenic tumour, it is very possible that FCDIII are caused by seizures or by the lesion causing the seizures. A subtype of FCDI has increased neuronal densities and decreased cortical thickness, with an abundance of cortical microcolumns (Blümcke *et al.*, 2010); the affected hemisphere is significantly smaller than the non-epileptogenic contralateral side. These observations support the concept that FCDI is a heterogeneous group of disorders that may result from late insult/injury to the developing cortex.

Group III.D: postmigrational microcephaly

Postmigrational microcephaly and the rationale for placing it in this section was discussed in the earlier 'Microcephaly' section.

Conclusion

In order to retain its utility for the clinician and physician scientist, both the framework and the content of this classification of Malformations of Cortical Development have been updated based upon recent scientific and clinical advances. Although complexity of this classification has increased, making it more cumbersome, accurate diagnoses are essential for both clinical and genetic counselling; thus, the authors believe that this level of complexity is currently necessary. Further updates (and, hopefully, simplification) will be required as information accumulates about the clinical, embryological, genetic and molecular biological aspects of these disorders. Unfortunately despite the many discoveries in genetics, advances in this field have been slowed by the limited access to human brain specimens for developmental neuropathology studies, such as cell lineage, gene expression and searches for somatic mosaicism, upon rare malformation of cortical developments. FCD is the exception, and this can be attributed to the flourishing of epilepsy surgery programmes. However, limited resources appear to be available for classical developmental neuropathology, with inadequate networks to facilitate access to post-mortem brain tissue containing malformations of cortical development. Hopefully, such an organization can be developed, and our knowledge will quickly increase to the point where these disorders are grouped according to the affected pathways; the tasks of both future authors and their readers will thereby be simplified.

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Supplementary material

Supplementary material is available at *Brain* online.

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Appendix 1 Full classification scheme

(I) MALFORMATIONS SECONDARY TO ABNORMAL NEURONAL AND GLIAL PROLIFERATION OR APOPTOSIS
- (A) SEVERE CONGENITAL MICROCEPHALY (MIC), pre-migrational reduced proliferation or excess apoptosis
  - (1) MIC with severe IUGR deficiency and short stature
    Clinically defined with AR inheritance
    - (a) Seckel syndrome with unknown cause (Shanske *et al*., 1997)
    - (b) MOPD syndromes with unknown cause
    - (c) Other MIC-IUGR syndromes
    - (d) Seckel syndrome with mutations in *ATR* at 3q22–q24 (O'Driscoll *et al*., 2003)
    - (e) MOPD type 2 with mutations in *PCNT* at 21q22.3 (Rauch *et al*., 2008)
    - (f) MOPD type 1 with mutations in *ORC1* at 1p32 (Bicknell *et al*., 2011)
    - (g) MOPD type 1 with mutations in *ORC4* at 2q22-q23 (Guernsey *et al*., 2011)
    - (h) MOPD type 1 with mutations in *ORC6* at 16q12 (Bernal and Venkitaraman, 2011)
    - (i) MOPD type 1 with mutations in *CDT1* at 16q24.3 (Bicknell *et al*., 2011*b*)
    - (j) MOPD type 1 with mutations in *CDC6* at 17q21.2 (Bicknell *et al*., 2011*a*)
  - (2) MIC with variable short stature (severe IUGR to mildly short), moderate to severe DD/ID, normal to thin cortex, SIMP, with/without callosal hypogenesis
    Genetically defined with AR inheritance
    - (a) Seckel syndrome or AR primary microcephaly (MCPH) with mutations in *CENPJ* at 13q12.12 (Al-Dosari *et al*., 2010)
    - (b) Seckel syndrome or MCPH with mutations in *CEP152* at 15q21.1 (Kalay *et al*., 2011)
  - (3) MIC with mildly short stature or normal growth, mild-moderate DD/ID, normal to thin cortex, with/without SIMP, with/without callosal hypogenesis and with/without focal PNH
    Clinically defined with AR inheritance
    - (a) AR primary microcephaly (MCPH) (Woods *et al*., 2005)
      Genetically defined with AR inheritance
    - (b) MCPH with mutations in *ASPM* at 1q31.3 (Bond *et al*., 2003; Shen *et al*., 2005; Desir *et al*., 2008)
    - (c) MCPH with mutations in *MCPH1* at 8p23.1 (Trimborn *et al*., 2004; Darvish *et al*., 2010)
    - (d) MCPH with mutations in *CDKRAP5* (Bond *et al*., 2005; W.B.D., in preparation)
    - (e) MCPH with mutations in *STIL* at 1p33 (Kumar *et al*., 2009)
  - (4) MIC with mildly short stature or normal growth, severe DD/ID, variable cortical development with SIMP or cortical dysgenesis and with/without ACC (includes genes with spectrum from SIMP to dysgenetic cortex or PMG)
    Clinically defined with AR or XL inheritance
    - (a) MIC with diffuse PMG
    - (b) MIC with asymmetric PMG
    - (c) MIC with atypical cortical dysgenesis
    Genetically defined with AR inheritance
    - (d) MCPH with mutations in *PNKP* at 19q13.33 (Shen *et al*., 2010)
    - (e) MCPH, MIC with diffuse PMG (MDP) or MIC with asymmetric PMG (MAP) with mutations in *WDR62* at 19q13.12 (Bilgüvar *et al*., 2010; Yu *et al*., 2010)
    - (f) MCPH, MDP (other cortical malformation) with mutations in *NDE1* at 16p13.11 (Alkuraya *et al*., 2011; Bakircioglu *et al*., 2011)
    - (g) MDP–MAP and ACC with mutations of *TBR2* (*EOMES*) at 3p24.1 (Baala *et al*., 2007)
  - (5) MIC with variable anomalies and less well characterized syndromes; with/without SIMP; with/without PNH, with/without CBLH
    Clinically defined with probable AR inheritance
    - (a) MIC with diffuse periventricular nodular heterotopia
    - (b) MIC with disproportionate cerebellar hypoplasia
    - (c) MIC (extreme) with jejunal atresia (Stromme *et al*., 1993)
    Genetically defined with AR inheritance
    - (d) MIC–PNH associated with mutations in *ARFGEF2* at 20q13.13 (Sheen *et al*., 2004; de Wit *et al*., 2009)
  - (6) MIC with severe DD/ID and evidence of degeneration, with/without mildly short stature, with/without enlarged extra-axial spaces, with/without ACC, with/without atypical cortical dysgenesis
    Clinically defined with AR inheritance
    - (a) MIC with enlarged extra-axial space
    - (b) MIC with enlarged extra-axial spaces and disproportionate cerebellar hypoplasia
    - (c) MIC due to foetal brain disruption with unknown cause

(continued)

Appendix 1 **Continued**

Genetically defined with AR inheritance
(d) Amish lethal microcephaly associated with mutations in *SLC25A19* at 17q25.1 (Rosenberg *et al*., 2002)
(e) MIC-capillary malformation syndrome (mutations in pending report)

(7) MIC with LIS (MLIS)—cortex thick or relatively thick, smooth white–grey border
Clinically defined with AR inheritance
(a) Barth MLIS syndrome
(b) Norman–Roberts MLIS syndrome
(c) MOPD1 variant with three-layer lissencephaly (Juric-Sekhar *et al*., 2011)
(d) MIC with lissencephaly, CBLH and Hirschsprung disease

(8) MIC with tissue loss and enlarged ventricles (hydrocephalus *ex vacuo* or hydranencephaly), with/without cortical dysplasia and with/without ACC
Clinically defined with presumed extrinsic (non-genetic) cause
(a) Foetal brain disruption sequence (Corona-Rivera *et al*., 2001)
Clinically defined with AR inheritance
(b) Familial foetal brain disruption-like syndrome with unknown cause
(c) Familial 'microhydranencephaly' with unknown cause (Behunova *et al*., 2010)
Genetically defined with AR inheritance
(d) Familial 'microhydranencephaly' associated with mutations of *MHAC* at 16p13.13–p12.2 (Kavaslar *et al*., 2000)

(B) MEGALENCEPHALY (MEG) including both congenital and early postnatal

(1) MEG with normal cortex (or presumably normal cortex)
Clinically defined with polygenic or AD inheritance
(a) Familial MEG
Genetically defined with AD inheritance
(b) Bannayan–Riley–Ruvalcaba syndrome, Cowden disease and MEG–autism with mutations in *PTEN* at 10q23.31 (Marsh *et al*., 1997; Marsh *et al*., 1999; Pilarski *et al*., 2011)
(c) Sotos syndrome with mutations in *NSD1* at 5q35.2–q35.3 (Türkmen *et al*., 2003)
(d) DD/ID, autism with *HEPACAM* mutations at 11q24.2 (AD, homozygous mutations cause AR megalencephaly with leukoencephalopathy and cysts) (López-Hernández *et al*., 2011)
(e) MEG, thumb anomalies and Weaver-like dysmorphism with dup 2p24.3 (includes *MYCN*)
Genetically defined with AR inheritance
(f) MACS syndrome with mutations in *RIN2* at 20p11.23 (Basel-Vanagaite *et al*., 2009)
Genetically defined with XL inheritance
(g) Simpson–Golabi–Behmel syndrome 1 with mutations in *GPC3* at Xq26.2 (Pilia *et al*., 1996)
(h) Simpson–Golabi–Behmel syndrome 2 with mutations in *OFD1* at Xp22.2 (Budny *et al*., 2006)
(i) MEG with DD/ID and seizures with mutations in *RAB39B* at Xq28 (Giannandrea *et al*., 2010)
Genetically defined with somatic mosaicism
(j) Proteus syndrome caused by somatic activating mutation in *AKT1* at 14q32.33 (Lindhurst *et al*., 2011)

(2) MEG with PNH—plus other anomalies
Clinically defined with AD or unknown inheritance
(a) MEG–PNH phenotype (Jan, 1999)

(3) MEG with PMG and other cortical dysgenesis
Clinically defined with unknown cause
(a) MCAP syndrome, includes MPPH (Mirzaa *et al*., 2004; Conway *et al*., 2007)
(b) Thanatophoric dysplasia or Apert syndrome with mutation of *FGFR3* at 4p16.3 (six-layered PMG-like cortex) (Hevner, 2005)

(C) CORTICAL DYSGENESIS WITH ABNORMAL CELL PROLIFERATION BUT WITHOUT NEOPLASIA

(1) Diffuse cortical dysgenesis
Genetically defined with AR inheritance
(a) PMSE syndrome with MEG, cortical dysgenesis including leptomeningeal glioneuronal heterotopia and cortical dysplasia mination with mutations in *STRADA (LYK5)* (Puffenberger *et al*., 2007)

(2) Focal and multifocal cortical and subcortical dysgenesis
Clinically defined with putative postzygotic mosaicism
(a) HMEG isolated (Flores-Sarnat, 2002; Salamon *et al*., 2006; Mathern *et al*., 2007)
(b) HMEG with neurocutaneous syndromes (Flores-Sarnat, 2002)
(c) FCD Type II with large, dysmorphic neurons (FCDIIa) (Blümcke *et al*., 2011)
(d) FCD Type II with large, dysmorphic neurons and balloon cells (FCDIIb), including transmantle dysplasia and bottom of sulcus dysplasia (Blümcke *et al*., 2011)

(continued)

Appendix 1 **Continued**

Genetically defined with AD inheritance
(e) Tuberous sclerosis with cortical hamartomas and mutations of *TSC1* at 9q34.13 (Jones *et al*., 1999; Crino *et al*., 2006)
(f) Tuberous sclerosis with cortical hamartomas and mutations of *TSC2* at 16p13.3 (Jones *et al*., 1999; Crino *et al*., 2006)
(g) Tuberous sclerosis with HMEG (Galluzzi *et al*., 2002)

(D) CORTICAL DYSPLASIAS WITH ABNORMAL CELL PROLIFERATION AND NEOPLASIA
(1) Neoplastic dysgenesis with primitive cells
(a) DNET
(2) Neoplastic dysgenesis with mature cells
(a) Ganglioglioma
(b) Gangliocytoma

(II) MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION
(A) MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES: PERIVENTRICULAR HETEROTOPIA
(1) Anterior predominate and diffuse PNH
Clinically defined with unknown cause
(a) Diffuse PNH with/without sparing of temporal horns
(b) Diffuse PNH composed of micronodules
(c) Diffuse PNH with frontonasal dysplasia (Guerrini and Dobyns, 1998)
(d) Anterior predominant PNH
(e) Anterior predominant PNH with fronto-perisylvian PMG (Wieck *et al*., 2005)
(f) Unilateral or bilateral isolated PNH
Genetically defined with AD inheritance (new mutations)
(g) Anterior PNH with duplication 5p15.1 (Sheen *et al*., 2003)
(h) Anterior or diffuse PNH with duplication 5p15.33 (Sheen *et al*., 2003)
(i) Diffuse (but variable) PNH with del 6q27 (W.B.D, in preparation)
(j) PNH and Williams syndrome with del 7q11.23, including *HIP1* and *YWHAG* (Ferland *et al*., 2006; Ramocki *et al*., 2010)
(k) PNH with del 4p15 (gene not identified) (Gawlik-Kuklinska *et al*., 2008)
(l) PNH with deletion 5q14.3–q15 (Cardoso *et al*., 2009)
(m) PNH and agenesis of the corpus callosum with del 1p36.22-pter (Neal *et al*., 2006)
Genetically defined with XL inheritance
(n) Bilateral PNH due to mutations of *FLNA*, with/without Ehlers–Danlos (Sheen *et al*., 2001; Parrini *et al*., 2006)
(o) PNH and Fragile X syndrome (Moro *et al*., 2006)
(2) Posterior predominant (temporal-trigonal) PNH
Clinically defined with unknown cause
(a) Posterior PNH only
(b) Posterior PNH with hippocampal dysgenesis, colpocephaly, anomalies of midbrain tectum or cerebellar hypoplasia
(c) Posterior PNH with posterior PMG (Wieck *et al*., 2005)
(3) Periventricular heterotopia, not nodular (unilateral or bilateral)
Clinically defined with unknown cause
(a) Diffuse PLH
(b) Frontal predominant PLH
(c) Posterior predominant PLH
(4) Ribbon-like heterotopia, bilateral undulating heterotopic band
Clinically defined with unknown cause
(a) Posterior predominant ribbon-like heterotopia
(b) Diffuse ribbon-like heterotopia

(B) MALFORMATIONS DUE TO GENERALIZED ABNORMAL TRANSMANTLE MIGRATION (radial and non-radial)
(1) Anterior predominant or diffuse classic (four-layered) LIS and SBH
Clinically defined with unknown cause
(a) Anterior predominant LIS with abrupt transition and cerebellar hypoplasia (previously LCHe)
(b) Anterior predominant or diffuse LIS (ILS)
Clinically defined with AR inheritance
(c) Anterior predominant LIS (ILS) with AR inheritance
(d) Winter–Tsukahara syndrome (Levin *et al*., 1993)
Clinically defined with AD (new mutation) inheritance
(e) Baraitser–Winter syndrome with anterior or diffuse LIS–SBH (Rossi *et al*., 2003)
(f) Anterior predominant LIS (ILS) or SBH with *DCX* mutation at Xq22.3–q23 (Dobyns *et al*., 1999)

(continued)

Appendix 1 Continued

(2) Posterior predominant or diffuse classic (four-layered) and two-layered (without cell-sparse zone) LIS and SBH
Clinically defined with unknown cause
(a) Posterior predominant or diffuse LIS with brainstem and cerebellar hypoplasia, with/without ACC (includes former LCHa, LCHc, LCHd, LCHf (Ross *et al*., 2001))
(b) Posterior predominant or diffuse LIS (ILS) (Pilz *et al*., 1998, Dobyns *et al*., 1999)
(c) Diffuse LIS with hair and nail anomalies (Celentano *et al*., 2006)
(d) Perisylvian (central) pachygyria (ILS)
(e) Ribbon like deep white matter heterotopia with/without ACC, thin overlying cortex
Clinically defined with AD inheritance
(f) Posterior predominant SBH (Deconinck *et al*., 2003)
Genetically defined with AD inheritance (new mutation)
(g) Posterior or diffuse LIS with cerebellar hypoplasia or LIS (ILS) with *TUBA1A* mutations at 12q12-q14 (Poirier *et al*., 2007; Kumar *et al*., 2010)
(h) Miller-Dieker syndrome (four-layered) with deletion 17p13.3 (*YWHAE* to *LIS1*) (Dobyns *et al*., 1991)
(i) Posterior or diffuse LIS (ILS, four-layered) or posterior SBH with *LIS1* deletions or mutations at 17p13.3 (Dobyns *et al*., 1993; Pilz *et al*., 1999)

(3) X-linked lissencephaly (three-layered, without cell-sparse zone) with callosal agenesis, ambiguous genitalia (XLAG)
Clinically defined with unknown cause
(a) XLAG-like syndrome with temporal-posterior predominant LIS, ACC, microphthalmia and midline cleft lip and palate
(b) XLAG with temporal-posterior predominant LIS and ACC with mutations in *ARX* at Xp22.13 (Bonneau *et al*., 2002)

(4) Reelin-type LIS (inverted cortical lamination, without cell-sparse zone)
Clinically defined with AR inheritance
(a) Frontal predominant mild LIS with severe hippocampal and CBLH (Kato *et al*., 1999)
Genetically defined with AR inheritance
(b) Frontal predominant mild LIS with severe hippocampal and CBLH with *RELN* mutation at 7q22 (Hong *et al*., 2000)
(c) Frontal predominant mild LIS with severe hippocampal and CBLH with *VLDLR* mutation at 9p24 (Boycott *et al*., 2005)

(5) Variant LIS (other rare types exist but are poorly characterized)

(C) MALFORMATIONS PRESUMABLY DUE TO LOCALIZED ABNORMAL LATE RADIAL OR TANGENTIAL TRANSMANTLE MIGRATION

(1) Subcortical heterotopia (other than band heterotopia or cortical infolding), all clinically defined with unknown cause
(a) Curvilinear transmantle heterotopia, with thinning of overlying cortex, decreased volume of affected hemisphere, with/without ACC, with/without basal ganglia anomalies (Barkovich, 1996)
(b) Multinodular subcortical heterotopia with thin overlying cortex, with/without PMG (Barkovich, 2000)
(c) Transmantle columnar heterotopia with/without PNH

(2) Sublobar Dysplasia, clinically defined with unknown cause (Tuxhorn *et al*., 2009)

(D) MALFORMATIONS DUE TO ABNORMAL TERMINAL MIGRATION AND DEFECTS IN PIAL LIMITING MEMBRANE

(1) Dystroglycan–laminin complex abnormalities with cobblestone malformation complex (COB), with or without congenital muscular dystrophy
Clinically defined with AR inheritance but causative gene unknown
(a) Walker–Warburg syndrome (Dobyns *et al*., 1985, 1997)
(b) Muscle–eye–brain syndrome (Santavuori *et al*., 1989; Haltia *et al*., 1997)
(c) Congenital muscular dystrophy with CBLH (Italian MEB)
Genetically defined with frontal predominant COB and AR inheritance
(d) WWS or MEB with *POMT1* mutation at 9q34.1 (Beltran-Valero de Bernabe *et al*., 2002; van Reeuwijk *et al*., 2006)
(e) WWS or MEB with *POMT2* mutation at 14q24.3 (van Reeuwijk *et al*., 2005; Mercuri *et al*., 2006)
(f) MEB with *POMGnT1* mutation at 1p34–p33 (Manya *et al*., 2003)
(g) WWS, FCMD or FCMD with retinal abnormality (MEB-like) with *FKTN* mutation at 9q31 (Beltran-Valero de Bernabe *et al*., 2003, Manzini *et al*., 2008, Yoshioka, 2009, Yis *et al*., 2011)
(h) WWS or MEB with *FKRP* mutation at 19q13.3 (Beltran-Valero de Bernabe *et al*., 2004)
(i) WWS or MEB with *LARGE* mutation at 22q12.3-q13.1 (van Reeuwijk *et al*., 2007)
Genetically defined with posterior predominate COB and AR inheritance
(j) Posterior predominant COB and CMD with *LAMA1A* mutation at 18p11.31
(k) Posterior predominant COB with *LAMC3* mutation at 9q33–q34 (lacks CMD) (Barak *et al*., 2011)

(2) Cobblestone malformations in CDG
Genetically defined with AR inheritance
(a) CHIME-like syndrome with frontal predominant COB with *SRD5A3* mutation at 4q12 (Al-Gazali *et al*., 2008; Cantagrel *et al*., 2010)

(continued)

Appendix 1 Continued

(b) Debré-type cutis laxa with frontal predominant COB and *ATP6V0A2* mutation at 12q24.3 (Kornak *et al*., 2008; Van Maldergem *et al*., 2008)

(3) Cobblestone malformation with no known glycosylation defect

(a) Frontal predominant COB with *GPR56* mutations at 16q13 ('bilateral frontoparietal polymicrogyria') (Piao *et al*., 2002, 2005)

(b) Walker-Warburg syndrome secondary to *COL4A1* mutations at 13q34 (Labelle-Dumais *et al*., 2011)

(4) Other syndromes with cortical dysgenesis and marginal glioneuronal heterotopia, but with normal cell types

Clinically defined with extrinsic or unknown cause

(a) Foetal alcohol syndrome

Clinically defined with AR inheritance

(b) Galloway–Mowat syndrome

(III) MALFORMATIONS DUE TO ABNORMAL POSTMIGRATIONAL DEVELOPMENT

(A) MALFORMATIONS WITH PMG OR CORTICAL MALFORMATIONS RESEMBLING PMG

(1) PMG (classic) with transmantle clefts (schizencephaly) or calcification

Clinically defined with clefts suggesting vascular pathogenesis or unknown cause

(a) Schizencephaly (Barkovich and Kjos, 1992)

(b) Septo-optic dysplasia with schizencephaly (Barkovich *et al*., 1989)

Clinically defined with prenatal viral exposure (especially CMV)

(c) Schizencephaly with positive neonatal CMV testing (Iannetti *et al*., 1998)

(d) Diffuse or patchy PMG with periventricular calcifications and positive neonatal CMV testing

(e) Diffuse, patchy or perisylvian PMG with hearing loss and positive neonatal CMV testing

Clinically defined with AR inheritance

(f) Familial schizencephaly with single unilateral or bilateral clefts (Haverkamp *et al*., 1995)

(g) Familial schizencephaly with multiple bilateral clefts

(h) Band-like calcifications with PMG (pseudo-TORCH) (Briggs *et al*., 2008)

Genetically defined with AR inheritance

(i) Band-like calcifications with PMG (pseudo-TORCH) with mutations of *OCLN1* at 5q13.2 (O'Driscoll *et al*., 2010)

(2) Polymicrogyria without clefts or calcifications classified by location

Clinically defined bilateral PMG without clefts of unknown cause

(a) Generalized PMG (Chang *et al*., 2004)

(b) Frontal PMG (Guerrini *et al*., 2000)

(c) Perisylvian PMG (Kuzniecky *et al*., 1993)

(d) Posterior PMG (lateral parieto-occipital) (Barkovich *et al*., 1999)

(e) Parasagittal PMG

(f) Parasagittal mesial occipital PMG (Guerrini *et al*., 1997)

Clinically defined unilateral PMG without clefts of unknown cause

(g) Hemispheric PMG (Chang *et al*., 2006)

(h) Perisylvian PMG (Chang *et al*., 2006)

(i) Focal PMG (Barkovich, 2010*a*)

(3) Syndromes with PMG (neuropathology may differ from classic PMG)

Clinically defined syndromes with AD inheritance

(a) Adams–Oliver syndrome AD form (Snape *et al*., 2009)

Clinically defined syndromes with AR inheritance

(b) Adams–Oliver syndrome AR form (Snape *et al*., 2009)

(c) Joubert syndrome and related disorders with PMG, includes Meckel–Gruber, Arima (cerebro-oculo-renal) and Joubert syndromes with causative genes unknown (Gleeson *et al*., 2004)

Clinically defined syndromes with XL inheritance (probable)

(d) Aicardi syndrome (Aicardi, 2005)

(e) Oculocerebrocutaneous (Delleman) syndrome (Moog *et al*., 2005)

Genetically defined with AD inheritance (new mutations)

(f) Fronto-parietal PMG, variable ACC and delayed myelination of anterior limb internal capsule with *TUBB2B* mutations at 6p25.2 (Jaglin *et al*., 2009)

(g) Fronto-parietal PMG, variable with *TUBB3* mutations at 16q24.3 (Poirier *et al*., 2010)

(h) Knobloch syndrome with high myopia, vitreoretinal degeneration, retinal detachment, occipital cephalocele and variable PMG with *COL18A1* mutations at 21q22.3 (Sertié *et al*., 2000)

(i) Aniridia, variable temporal PMG, absent anterior commissure and pineal gland, and variable CBLH with *PAX6* mutations at 11p13 (Mitchell *et al*., 2003; Graziano *et al*., 2007)

(j) Perisylvian PMG with deletion 1p36.3 (gene not identified) (Dobyns *et al*., 2008)

(k) Perisylvian PMG with deletion 22q11.2 (gene not identified) (Cramer *et al*., 1996)

(continued)

Appendix 1 Continued

Genetically defined with AR inheritance
- (l) Goldberg–Shprintzen (megacolon) syndrome with mutations of *KIAA1279* at 10q22.1 (Brooks *et al*., 2005)
- (m) Joubert syndrome with variable (low penetrance) PMG and *AHI1* mutations at 6q23.3 (Dixon-Salazar *et al*., 2004; Valente *et al*., 2006)
- (n) Meckel–Gruber syndrome with variable (low penetrance) PMG and *TMEM216* mutations at 11q12.2 (Valente *et al*., 2010)
- (o) Generalized (versus perisylvian) PMG, ACC and optic nerve hypoplasia with *TUBA8* mutations at 22q11.21 (Abdollahi *et al*., 2009)
- (p) Perisylvian PMG, ACC, delayed myelination of anterior limb internal capsule and cerebellar vermian hypoplasia with mutation of *TBR2* (*EOMES*) at 3p24.1 (Baala *et al*., 2007)
- (q) Warburg Micro syndrome with mutations of *RAB3GAP1* at 2q21.3 (Morris-Rosendahl *et al*., 2010)
- (r) Warburg Micro syndrome with mutations of *RAB3GAP2* at 1q41 (Borck *et al*., 2011)
- (s) Warburg Micro syndrome with mutations of *RAB18* at 10p12.1 (Bem *et al*., 2011)

Genetically defined with XL inheritance
- (t) Perisylvian PMG, rolandic seizures and speech-language dyspraxia with *SRPX2* at Xq22.1 mutations (Roll *et al*., 2006, 2010)
- (u) Perisylvian PMG, mild MIC and thin body habitus with *NSDHL* mutation at Xq28 (McLarren *et al*., 2010)
- (v) Perisylvian PMG with Xq27 locus (gene not identified) (Santos *et al*., 2008)
- (w) Perisylvian PMG with Xq28 locus (gene not identified) (Villard *et al*., 2002)

(B) CORTICAL DYSGENESIS SECONDARY TO INBORN ERRORS OF METABOLISM (neuropathology differs from classic PMG)

Genetically and biochemically defined with AR inheritance

(1) Mitochondrial and pyruvate metabolic disorders
- (a) Non-ketotic hyperglycinaemia with mutations of *GLDC* at 9p24.1, *GCSH* at 16q23.2 or *AMT* at 3p21.31
- (b) Multiple Acyl-CoA dehydrogenase deficiency (Glutaric aciduria type II) with mutations of *ETFA* at 15q24.2-q24.3, *ETFB* at 19q13.41 or *ETFDH* at 4q32.1 (Govaert *et al*., 2004)

(2) Peroxisomal disorders
- (a) Zellweger syndrome with mutation of many genes involved in peroxisomal biogenesis (Volpe and Adams, 1972; Steinberg *et al*., 2006)
- (b) Neonatal adrenoleukodystrophy with mutation of many genes involved in peroxisomal biogenesis (Kamei *et al*., 1993)
- (c) D-Bifunctional protein deficiency with *HSD17B4* mutation at 5q2 (Grønborg *et al*., 2010)

(C) FOCAL CORTICAL DYSPLASIAS (WITHOUT DYSMORPHIC NEURONS) DUE TO LATE DEVELOPMENTAL DISTURBANCES

Clinically/histologically defined and sporadic

(1) Minor malformations of Cortical Development (mMCD)

(2) Type I FCD
- (a) Abnormal radial cortical lamination (Blümcke *et al*., 2011)
- (b) Abnormal tangential cortical lamination (Blümcke *et al*., 2011)
- (c) Abnormal radial and tangential lamination (Blümcke *et al*., 2011)

(3) Type III FCD
- (a) Associated with hippocampal sclerosis (Blümcke *et al*., 2011)
- (b) Associated with tumors (Blümcke *et al*., 2011)
- (c) Associated with vascular malformations (Blümcke *et al*., 2011)
- (d) Associated with other principal lesions during early life (Blümcke *et al*., 2011)

(D) POSTMIGRATIONAL DEVELOPMENTAL MICROCEPHALY (PREVIOUSLY POSTNATAL MIC) WITH BIRTH OFC –3 SD OR LARGER, LATER OFC BELOW –4 SD AND NO EVIDENCE OF BRAIN INJURY

(1) Postmigrational MIC with limited functional deficits

Clinically defined
- (a) Postmigrational MIC with no cause or syndrome identified

Genetically defined with AD inheritance (sporadic new mutations)
- (b) MIC and mild ID with *SHH* mutation (Ginocchio *et al*., 2008)
- (c) MIC and variable ACC with deletion 1q43q44 (includes *AKT3*) (Hill *et al*., 2007)

(2) Postmigrational MIC with broad functional deficits consistent with a 'developmental encephalopathy' (Angelman-like, Rett-like class of disorders)

Clinically defined with AR inheritance
- (a) PEHO syndrome (Salonen *et al*., 1991; Vanhatalo *et al*., 2002)

Genetically defined with AD inheritance (sporadic new mutations)
- (b) Pitt–Hopkins syndrome with mutations of *TCF4* at 18q21.1 (Zweier *et al*., 2007)
- (c) FOXG1 syndrome with deletions or mutations of *FOXG1* at 14q13 (Kortüm *et al*., 2011)
- (d) Duplication of FOXG1 at 14q13 (Brunetti-Pierri *et al*., 2011)

(continued)

Appendix 1 **Continued**

Genetically defined with AD inheritance (or pathogenic *de novo* copy number variant) and imprinting effects

(e) Maternal duplication 15q11.2 (Kitsiou-Tzeli *et al*., 2010)

(f) Angelman syndrome with maternally deletion 15q11.2 or mutation of *UBE3A* at 15q11.2 (Matsuura *et al*., 1997)

Genetically defined with AR inheritance

(g) Pitt–Hopkins like syndrome with mutations of *NRXN1* at 2p16.3 (Zweier *et al.*, 2009)

(h) Pitt–Hopkins-like syndrome with mutations of *CNTNAP2* at 7q35-q36 (Zweier *et al.*, 2009)

(i) Pontocerebellar hypoplasia with mutations of *TSEN54* at 17q25.1, *TSEN2* at 3p25.1, *TSEN34* at 19q13.4, *RARS2* at 6q16.1 (Namavar *et al.*, 2011)

Genetically defined with XL inheritance

(j) Rett syndrome with mutations of *MECP2* at Xq28 (Amir *et al.*, 1999)

(k) Angelman-like syndrome with mutations of *SLC9A6* at Xq26.3 (Gilfillan *et al.*, 2008)

(l) X-linked mental retardation and autistic features with mutations of *JARID1C* at xp11.22–p11.21 (Jensen *et al.*, 2005; Abidi *et al.*, 2008)

(m) X-linked MIC with disproportionate cerebellar hypoplasia with mutations of *CASK* at Xp11.4 (in females) (Najm *et al.*, 2008)

ACC = agenesis of corpus callosum; AD = autosomal dominant inheritance; AR = autosomal recessive inheritance; CBLH = cerebellar hypoplasia; CDG = congenital disorders of glycosylation; CHIME = coloboma, heart defect, ichthyosiform dermatosis, mental retardation, ear anomalies; CMD = congential muscular dystrophy; CMV = cytomegalovirus; COB = cobblestone complex; DD/ID = developmental delay/intellectual disability; DNET = dysembryoplastic neuroepithelial tumour; FCMD = Fukuyama congenital muscular dystrophy; HMEG = hemimegalencephaly; ILS = isolated lissencephaly syndrome; IUGR = intrauterine growth retardation; LCH = lissencephaly with cerebellar hypoplasia; LIS = lissencephaly; MACS = macrocephaly, alopecia, cutis laxa, scoliosis; MAP = microcephaly with asymmetric polymicrogyria; MCPH = autosomal recessive primary microcephaly; MDP = microcephaly with diffuse polymicrogyria; MEB = muscle–eye–brain syndrome; MEG = megalencephaly; MIC = microcephaly; MLIS = microcephaly with lissencephaly; MOPD = microcephalic osteodysplastic primordial dwarfism syndrome; MPPH = megalencephaly with polymicrogyria, polydactyly and hydrocephalus; PEHO = progressive encephalopathy with oedema, hypsarrhythmia and optic atrophy; PLH = periventricular laminar heterotopia; PMG = polymicrogyria; PMSE = polyhydramnios, megalencephaly and symptomatic epilepsy; PNH = periventricular nodular heterotopia; SBH = subcortical band heterotopia; SIMP = simplified gyral pattern; WWS = Walker–Warburg syndrome; XL = X-linked inheritance; XLAG = X-linked lissencephaly with agenesis of corpus callosum and ambiguous genitalia.